Complete Summary

GUIDELINE TITLE

Treatment of chronic myeloid leukemia with imatinib.

BIBLIOGRAPHIC SOURCE(S)

Hematology Disease Site Group. Walker I, Makarski J, Stevens A, Meyer RM. Treatment of chronic myeloid leukemia with imatinib. Toronto (ON): Cancer Care Ontario (CCO); 2004 Jul 16. 27 p. (Practice guideline report; no. 6-15). [39 references]

GUIDELINE STATUS

This is the current release of the guideline.

The FULL REPORT, initially the full original Guideline, over time will expand to contain new information emerging from their reviewing and updating activities.

Please visit the Cancer Care Ontario Web site for details on any new evidence that has emerged and implications to the guidelines.

COMPLETE SUMMARY CONTENT

SCOPE

DISEASE/CONDITION(S)

Chronic myeloid leukemia

GUIDELINE CATEGORY

Assessment of Therapeutic Effectiveness
Treatment

CLINICAL SPECIALTY

Hematology
Oncology

INTENDED USERS

Physicians

GUIDELINE OBJECTIVE(S)

To evaluate the role of imatinib (STI571, Gleevec™, Glivec®) in treating patients with chronic myeloid leukemia, including those with accelerated and blastic phases of the disease

TARGET POPULATION

Adult patients with chronic myeloid leukemia, including those with accelerated and blastic phases of the disease

INTERVENTIONS AND PRACTICES CONSIDERED

Imatinib (STI571, Gleevec™, Glivec®) therapy

MAJOR OUTCOMES CONSIDERED

- Survival
- Quality of life
- Duration of treatment response
- Toxicity
- Hematologic response
- Cytogenetic or molecular response

METHODOLOGY

METHODS USED TO COLLECT/SELECT EVIDENCE

Hand-searches of Published Literature (Primary Sources)
Hand-searches of Published Literature (Secondary Sources)
Searches of Electronic Databases

DESCRIPTION OF METHODS USED TO COLLECT/SELECT THE EVIDENCE

MEDLINE (1985 through July 2003), MEDLINE® In-Process & Other Non-Indexed Citations (PREM; formerly known as PREMEDLINE) (last searched July 10, 2003), CANCERLIT (1985 through October 2002), and The Cochrane Library (2003, Issue 2) databases were searched. The literature search strategy is shown in Appendix I of the original guideline document. The searches were limited to human and the English language. In addition, conference proceedings of the 1999-2003 annual meetings of the American Society of Clinical Oncology and of the 1999-2002

annual meetings of the American Society of Hematology were searched for abstracts of relevant trials. The National Guideline Clearinghouse (http://www.guideline.gov) and Canadian Medical Association Infobase (http://mdm.ca/cpgsnew/cpgs/index.asp) databases were searched for evidence-based practice guidelines. Relevant articles and abstracts were selected and reviewed by two reviewers, and the reference lists from these sources were searched for additional trials, as were the reference lists from relevant review articles. Personal files were also searched.

Inclusion Criteria

For literature searches conducted from March 2001 to October 2002, articles were selected for inclusion in this systematic review of the evidence if they were fully published reports or published abstracts of:

1. Randomized controlled trials comparing imatinib with conventional treatments in patients with chronic myeloid leukemia (CML) of any phase.
2. Phase I or II trials reporting the safety and efficacy of imatinib in patients with CML of any phase.

For literature searches conducted from November 2002 onward, articles were selected for inclusion if they were fully published reports or published abstracts of:

1. Randomized controlled trials comparing imatinib with conventional treatments in patients with CML of any phase.
2. Systematic reviews or practice guidelines assessing imatinib in patients with CML of any phase.

Exclusion Criteria

For literature searches conducted from March 2001 to October 2002, reports excluded from consideration included:

1. Pilot studies describing use of imatinib in combination with other drugs.
2. Studies investigating the role of imatinib post-transplantation.

For literature searches conducted from November 2002 onward, reports excluded from consideration included:

1. Studies investigating the role of imatinib post-transplantation.

NUMBER OF SOURCE DOCUMENTS

Twelve non-randomized trials (2 phase I and 10 phase II), one randomized controlled trial (6 reports), and one report of a systematic review were identified and reviewed.

METHODS USED TO ASSESS THE QUALITY AND STRENGTH OF THE EVIDENCE

Expert Consensus (Committee)

RATING SCHEME FOR THE STRENGTH OF THE EVIDENCE

Not applicable

METHODS USED TO ANALYZE THE EVIDENCE

Systematic Review with Evidence Tables

DESCRIPTION OF THE METHODS USED TO ANALYZE THE EVIDENCE

Because of the heterogeneity of the patient groups included in reported trials, inconsistent reporting of outcomes of interest, and varying criteria used to define outcome measures, the results of the trials were not pooled.

METHODS USED TO FORMULATE THE RECOMMENDATIONS

Expert Consensus

DESCRIPTION OF METHODS USED TO FORMULATE THE RECOMMENDATIONS

The development of imatinib has been based on a sound understanding of the molecular pathogenesis of chronic myeloid leukemia (CML) and a rational process of determining how that process might be pharmacologically altered. The results of testing imatinib in patients with CML reinforce the concept that drugs designed to specifically target key steps in the molecular pathogenesis of a malignancy may be associated with anti-tumour effects, while minimizing toxicity to other tissues. The Hematology Disease Site Group (DSG) considered the available data to represent an important advance in treating patients with CML, and the DSG's interpretation of the role of imatinib evolved as new data emerged from testing this medication in various situations and with different trial designs.

Based on data reported in Part 1 of the Results section in the original guideline document, the initial conclusions of the DSG that were reached in May 2002 remain valid given the data that have become available since that time.

RATING SCHEME FOR THE STRENGTH OF THE RECOMMENDATIONS

Not applicable

COST ANALYSIS

The National Institute for Health and Clinical Excellence (NICE) completed an economic evaluation in their technology assessment report, not based on systematic review methodology. The National Institute for Health and Clinical Excellence concluded that, in comparison with interferon, first-line treatment with imatinib would result in an incremental cost-effectiveness ratio (ICER) of about 26,000 pounds sterling (range 13,500-52,000 pounds sterling) per quality-adjusted life year (QALY). Comparison values provided for perspective included incremental cost-effectiveness ratios of 87,000 pounds sterling per QALY when first-line therapy with imatinib was compared with hydroxyurea and over

1,000,000 pounds sterling per QALY when first-line therapy with interferon was compared with hydroxyurea.

METHOD OF GUIDELINE VALIDATION

External Peer Review
Internal Peer Review

DESCRIPTION OF METHOD OF GUIDELINE VALIDATION

Practitioner feedback was obtained through a mailed survey of 100 practitioners in Ontario (63 hematologists and 37 medical oncologists). The survey consisted of items evaluating the methods, results, and interpretive summary used to inform the draft recommendations and whether the draft recommendations should be approved as a practice guideline. Written comments were invited. The practitioner feedback survey was mailed out on November 17, 2003. Follow-up reminders were sent at two weeks (post card) and four weeks (complete package mailed again). The Hematology Disease Site Group (DSG) reviewed the results of the survey.

The practice guideline report was circulated to members of the Practice Guidelines Coordinating Committee for review and approval. Eight of 14 members returned ballots (one member was also a member of the Hematology DSG and did not review the report).

This practice guideline reflects the integration of the draft recommendations with feedback obtained from the external review process. It has been approved by the Hematology DSG and by the Practice Guidelines Coordinating Committee.

RECOMMENDATIONS

MAJOR RECOMMENDATIONS

- Imatinib is recommended as first-line therapy in newly diagnosed patients with Philadelphia chromosome-positive chronic myeloid leukemia. The initial recommended dose of therapy is 400 milligrams (mg), given orally, once daily. For patients who do not demonstrate a complete hematologic response after three months of therapy or at least a minor cytogenetic response after 12 months of therapy, the dose of imatinib should be increased to 400 mg, given orally, twice daily.
- Imatinib is recommended for patients who have become refractory to or intolerant of previous therapy (e.g., interferon +/- cytarabine, hydroxyurea) or who have disease progression to accelerated or myeloid blastic phases of the disease. For patients with accelerated or myeloid blastic phases of the disease, the starting dose of imatinib should be 600 mg, given orally, once daily with an increase in dose to 400 mg, given orally, twice daily, if an adequate hematologic or cytogenetic response is not observed.

CLINICAL ALGORITHM(S)

None provided

EVIDENCE SUPPORTING THE RECOMMENDATIONS

TYPE OF EVIDENCE SUPPORTING THE RECOMMENDATIONS

The recommendations are supported by non-randomized trials, a randomized controlled trial and a systematic review.

BENEFITS/HARMS OF IMPLEMENTING THE GUIDELINE RECOMMENDATIONS

POTENTIAL BENEFITS

- In the randomized controlled trial reported in article form (referred to as the International Randomized Study of Interferon and STI571 study), 1106 patients with newly diagnosed chronic myeloid leukemia were randomized to receive imatinib or interferon plus cytarabine. After a median follow-up of 19 months, the group randomized to receive imatinib, in contrast to the combined therapy, had a superior rate of complete hematologic responses (95.3% versus 55.5%; $p<0.001$), major cytogenetic responses (85.2% versus 22.1%; $p<0.001$), complete cytogenetic responses (73.8% versus 8.5%; $p<0.001$), 18-month progression-free survival (92.1% versus 73.5%; $p<0.001$), and freedom from progression to accelerated or blastic phase at 18 months (96.7% versus 91.5%; $p<0.001$); despite these benefits, no difference in overall survival between the groups (97.2% versus 95.1%; $p=0.16$) has been detected to date. Superior QoL assessments were observed in patients randomized to receive imatinib. In patients with a complete cytogenetic response, preliminary data indicate superiority of imatinib for molecular response, the clinical significance of which is evolving and not addressed at this time.
- Imatinib has been tested in three phase II trials in patients who are refractory to or intolerant of interferon. In a trial involving 454 patients treated for a median of 17.9 months, complete hematologic responses were observed in 95% of patients and major cytogenetic responses in 60% of patients at the time of analysis. At 18 months, the estimated probability of progression-free survival was 89%, and the estimated survival was 95%. In a second trial (abstract), 194 patients followed for more than 6 months were observed to have similar complete hematologic (93%) and cytogenetic (44% major, 28% complete) responses.
- Imatinib has been tested in one phase II trial in 181 patients who have chronic myeloid leukemia in accelerated phase. The first 62 patients (34%) were initially treated with 400 mg daily, and subsequent patients were initially treated with 600 mg daily. With a median treatment duration of 10 months for patients receiving 400 mg daily and 11 months for those receiving 600 mg daily, 82% of patients had a hematologic response, with 69% being sustained for at least four weeks. The estimated duration of sustained response was greater than 12 months in 70% of patients, and estimated overall survival at 12 months was 74%. With multivariate analysis, factors most strongly predicting a longer time to disease progression were a hemoglobin of at least 100 g per litre ($p=0.0002$) and a starting imatinib dose of 600 mg ($p=0.0005$).
- Imatinib has been tested in one phase I trial and two phase II trials in patients who have chronic myeloid leukemia in blastic phase. In the phase I

trial, a response, defined as a complete hematologic response or a reduction in marrow blasts to 15% or less, was observed in 55% of patients with myeloid disease and 70% of patients with lymphoid disease. Of the 55% of responding patients with myeloid blastic crisis, 43% experienced a relapse at a median of 84 days of treatment (range, 42-194 days); of 70% of responding patients with lymphoid blastic crisis or Philadelphia chromosome-positive acute lymphoblastic leukemia, 86% experienced a relapse at a median of 58 days of treatment (range 42-123 days). In a phase II trial, 260 patients with chronic myeloid leukemia in myeloid blastic crisis were treated with imatinib 400 mg daily (37 patients) or 600 mg per day (223 patients). With a median duration of therapy of about four months, hematologic responses were observed in 119 patients (52%) and were sustained for four or more weeks in 70 patients (31%). Major cytogenetic responses were observed in 37 patients (16%) and were complete in 17 patients (7%). The estimated median duration of hematologic response was 10 months, and estimated median survival was 6.9 months.

POTENTIAL HARMS

Imatinib is well tolerated at a dose of 400 mg daily with no more than mild or moderate (National Cancer Institute-Common Toxicity Criteria [NCI-CTC] grades 1 or 2) toxicities in the vast majority of patients. These toxicities are predominantly gastrointestinal (nausea, diarrhea, and dyspepsia). Other toxicities include fatigue, edema, myalgias, arthralgias, mild neutropenia, and thrombocytopenia; the latter hematologic toxicities are more common in patients in the accelerated or blastic phase of the disease. Life-threatening side effects (grade 4) are rare. There are no reports evaluating long-term toxicities.

QUALIFYING STATEMENTS

QUALIFYING STATEMENTS

- The Hematology Disease Site Group considers the current evidence insufficient to make recommendations regarding the duration of imatinib therapy for those in chronic phase, whether or not they are in complete hematologic and major cytogenetic remission. It is unclear whether alternative therapy would improve the outcome of patients who have failed to attain major cytogenetic remissions or who relapse from previous remission. At present, the Hematology Disease Site Group feels that all patients taking imatinib therapy could be maintained on this therapy, with or without additional therapy, until further information becomes available. The role of additional cytogenetic monitoring, other than that performed at 12 months as per the International Randomized Study of Interferon and STI571 trial or to assist in the decision-making process for transplantation, is at present uncertain. Eventually, failure to attain a major cytogenetic remission may become an indication for alternative or combined therapy when such therapies become established.
- For patients with chronic phase chronic myeloid leukemia who have had a hematologic and cytogenetic response to interferon (+/- cytarabine) and are tolerating this therapy, treatment decisions are more difficult. Patients should be aware of data demonstrating that, in comparison with interferon (+/- cytarabine); imatinib is associated with superior effectiveness and quality-of-

life assessments and less toxicity. These benefits must be weighed against the lack of data describing the long-term effects of this medication and knowledge about potential drug resistance. The Hematology Disease Site Group considers it reasonable for physicians to recommend a change in therapy from interferon (+/- cytarabine) to imatinib, as many patients cannot remain on interferon-containing regimens long term, imatinib is associated with the benefits described above, and survival with imatinib therapy is unlikely to be inferior.

- The clinical importance of observed molecular responses in newly diagnosed patients with chronic phase chronic myeloid leukemia who achieved complete cytogenetic responses with imatinib therapy is evolving and was not addressed at this time.
- The place of bone marrow transplantation in the initial treatment of chronic myeloid leukemia has not been assessed in randomized trials. Prior imatinib therapy does not appear to compromise the results of transplantation except possibly through delays in its initiation. Patients for whom transplantation will be recommended as a second-line treatment after failure to achieve a major cytogenetic remission with imatinib should have a cytogenetic analysis testing no later than 12 months following the commencement of therapy.
- To date, the Hematology Disease Site Group has not reached consensus on the management of patients with chronic myeloid leukemia that has progressed into a lymphoid blastic phase. Preliminary results of testing imatinib in these patients have shown that any responses are usually of very short duration. The potential to use other treatments, such as regimens commonly used to treat acute lymphoblastic leukemia, should be considered.
- Care has been taken in the preparation of the information contained in this document. Nonetheless, any person seeking to apply or consult the practice guideline is expected to use independent medical judgment in the context of individual clinical circumstances or seek out the supervision of a qualified clinician. Cancer Care Ontario makes no representation or warranties of any kind whatsoever regarding their content or use or application and disclaims any responsibility for their application or use in any way.

IMPLEMENTATION OF THE GUIDELINE

DESCRIPTION OF IMPLEMENTATION STRATEGY

An implementation strategy was not provided.

INSTITUTE OF MEDICINE (IOM) NATIONAL HEALTHCARE QUALITY REPORT CATEGORIES

IOM CARE NEED

Living with Illness

IOM DOMAIN

Effectiveness

IDENTIFYING INFORMATION AND AVAILABILITY

BIBLIOGRAPHIC SOURCE(S)

Hematology Disease Site Group. Walker I, Makarski J, Stevens A, Meyer RM. Treatment of chronic myeloid leukemia with imatinib. Toronto (ON): Cancer Care Ontario (CCO); 2004 Jul 16. 27 p. (Practice guideline report; no. 6-15). [39 references]

ADAPTATION

Not applicable: The guideline was not adapted from another source.

DATE RELEASED

2004 Jul 16

GUIDELINE DEVELOPER(S)

Program in Evidence-based Care - State/Local Government Agency [Non-U.S.]

GUIDELINE DEVELOPER COMMENT

The Program in Evidence-based Care (PEBC) is a project supported by Cancer Care Ontario and the Ontario Ministry of Health and Long-Term Care.

SOURCE(S) OF FUNDING

Cancer Care Ontario
Ontario Ministry of Health and Long-Term Care

GUIDELINE COMMITTEE

Provincial Hematology Disease Site Group

COMPOSITION OF GROUP THAT AUTHORED THE GUIDELINE

For a current list of past and present members of the Hematology Disease Site Group, please see the Cancer Care Ontario Web site.

FINANCIAL DISCLOSURES/CONFLICTS OF INTEREST

Members of the Hematology Disease Site Group disclosed potential conflict of interest information.

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GUIDELINE AVAILABILITY

Electronic copies: Available in Portable Document Format (PDF) from the Cancer Care Ontario Web site.

AVAILABILITY OF COMPANION DOCUMENTS

The following are available:

- Treatment of chronic myeloid leukemia with imatinib. Summary. Toronto (ON): Cancer Care Ontario (CCO), 2004 Jul. Various p. (Practice guideline; no. 6-15). Electronic copies: Available in Portable Document Format (PDF) from the Cancer Care Ontario Web site.
- Browman GP, Levine MN, Mohide EA, Hayward RSA, Pritchard KI, Gafni A, et al. The practice guidelines development cycle: a conceptual tool for practice guidelines development and implementation. J Clin Oncol 1995;13(2):502-12.

PATIENT RESOURCES

None available

NGC STATUS

This summary was completed by ECRI on September 9, 2005. The information was verified by the guideline developer on October 3, 2005.

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